Willful modulation of brain activity in disorders of consciousness

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ABSTRACT

Background. Differential diagnosis of patients with disorders of consciousness is challenging. With misdiagnosis rates of about 40%, novel methodologies are required to complement bedside testing, particularly when the patient's capacity to produce behavioral signs of awareness is diminished

Methods. . We studied 54 patients with disorders of consciousness at 2 major referral centers in the UK (Cambridge) and Belgium (Liege). We used fMRI to assess each patient's ability to generate willful, neuroanatomically specific, blood oxygenation level dependent responses during two established mental imagery tasks. A novel technique was then developed to establish whether such tasks could be used to communicate 'yes/no' answers to simple questions.

Results. Of 54 patients, 5 were able to willfully modulate their brain activation. In three cases, additional bedside testing revealed some sign of awareness, but in the remaining two no voluntary behavior could be detected *via* clinical assessment. Moreover, this technique was used in a patient to answer 'yes/no' questions in the fMRI scanner. In contrast, it remained impossible to establish any form of communication at the bedside.

Conclusion. These results demonstrate that a small proportion of vegetative and minimally conscious patients show brain activation reflecting some awareness and cognition. Careful clinical examination will result in reclassification of the state in some of these patients. This technique may be useful in establishing basic communication with ostensibly unresponsive patients.

In recent years, improvements in intensive care have lead to an increase in the number of patients who survive severe brain injury. Although some of these patients go on to make a good recovery, others awaken from the acute comatose state, but fail to show any signs of awareness. If repeated examinations yield no evidence of sustained, reproducible, purposeful or voluntary behavioral response to visual, auditory, tactile or noxious stimuli, a diagnosis of vegetative state (VS) – or 'wakefulness without awareness' – is made.[1-5] Some VS patients remain in this condition permanently. Others, however, progress to show inconsistent, but reproducible signs of awareness, including command following, but fail to show interactive communication. In 2002, the Aspen Neurobehavioral Conference Workgroup coined the term 'minimally conscious state' (MCS) to describe such patients, thereby adding a new clinical entity to the spectrum of disorders of consciousness.[6]

The clinical assessment of VS and MCS patients has two main goals. First, to determine whether the patient retains any purposeful response to stimulation, albeit inconsistent, suggesting they are at least partially aware. Crucially, this decision separates VS from MCS patients and has, therefore, implications for the subsequent care of the patient and rehabilitation, as well as legal and ethical decision-making. Unfortunately, the behavior elicited by these patients is often ambiguous, inconsistent and typically constrained by varying degrees of paresis making it very challenging to disentangle purely reflexive from voluntary behaviors. Nevertheless, in the absence of any absolute measure, the presence of awareness has to be *inferred* from a patient's motor responsiveness, a fact that undoubtedly contributes to the high rate of diagnostic error (~40%) in this patient group.[7-9]

The second goal of clinical assessment is to harness and nurture any available response, through intervention, into a form of reproducible communication, however rudimentary. The acquisition of any interactive and functional verbal or non-verbal method of communication represents an important milestone. Clinically, consistent and repeatable communication demarcates the upper boundary of MCS.[6]

In this report, we present the results of a 3-year study in which functional magnetic resonance imaging (fMRI) data was routinely used in the evaluation of a large group (N=54) of patients who were diagnosed clinically as VS or MCS. In the light of a previous single-case study demonstrating intact awareness in a patient who behaviorally met the clinical criteria for VS[10], our investigation had two main aims. First, to determine what proportion of this larger group of patients could also reliably and repeatedly modulate their fMRI responses to indicate preserved awareness. Second, to develop and validate a novel paradigm that would allow such patients to functionally communicate ‘yes’ and ‘no’ responses by modulating their own brain activity, without training and without the need for any motor response.

Methods and Statistical Analysis

Participants. An anecdotal convenience sample of 54 severely brain injured patients, including 23 VS and 31 MCS patients, underwent the motor and spatial imagery tasks. (See Table 1 for patient details, and the Appendix for inclusion criteria.) Written consent for all patients was obtained from the legal guardian. The motor and spatial imagery tasks have been well validated in healthy volunteers[10-12] and are known to produce distinct fMRI activity in the supplementary motor area (SMA) and the parahippocampal gyrus (PPA).

The novel communication paradigm was first tested for feasibility and robustness in 16 healthy volunteers (7 female) with no history of neurological disorder. Once validated, the task was given to one patient (L23 in Table 1 and Figure 1) who had been diagnosed as permanently vegetative 17 months after a road-traffic accident, a diagnosis that was confirmed by a month-long specialized assessment 3.5 years post-injury. At the time of admission for fMRI scanning (5 years post-ictus) the patient was assumed to remain vegetative, although extensive behavioral testing subsequent to the fMRI scan revealed reproducible, but inconsistent, responses indicative of a MCS. (See the Appendix for detailed patient history and clinical assessment.)

Imagery task. While in the fMRI scanner, all patients were asked to perform two imagery tasks. In the motor imagery task they were instructed to imagine standing still on a tennis court and to swing their arm to "hit the ball" back and forth to an imagined instructor. In the spatial navigation task, participants were instructed to imagine navigating the streets of a familiar city or to imagine walking from room to room in their home and to visualize all that they would "see" if they were there. First, two *localizer* scans were conducted in which the patients were instructed to alternate 30 s epochs of mental imagery with 30 s epochs of rest. Each scan included 5 rest-imagery cycles. The beginning of each imagery epoch was aurally cued by the words '*tennis*' or '*navigation*', while rest epochs were cued with '*relax*'.

Communication task. Following the localizer scans, all 16 volunteers and 1 patient underwent a set of *communication* scans in which they attempted to answer questions by modulating their brain activity. Prior to each scan, participants were asked a 'yes/no' question (e.g. "do you have any brothers?") and instructed to respond during the scan by producing one type of imagery for 'yes' and the other for 'no.' The nature of the questions ensured that the experimenters would not know the correct answers prior to judging the fMRI data. Participants were required to respond by producing whichever imagery corresponded to the answer that they wanted to convey. Question scans were identical to localizers with the exception that the same neutral word '*answer*' was used to cue each response (rest epochs were cued with '*relax*'). Cues were delivered once, at the beginning of each epoch.

The 16 healthy volunteers performed three communication scans (i.e. 3 questions), while, to maximize statistical power, the patient underwent six (i.e. 6 questions).

Data Analysis. Analyses were performed using FSL 4.1.[13] Each scan underwent standard fMRI pre-processing steps (see Appendix for fMRI acquisition parameters and pre-processing). For each scan, a general linear model contrasting epochs of active imagery to epochs of rest was computed. All contrasts were limited to the brain locations falling within the SMA and PPA, as defined in the Harvard-Oxford Cortical Structural Atlas (available in FSL), and thresholded, with Gaussian Random Fields theory, at a cluster level of $Z > 2.3$, $p < 0.05$ (corrected). The defined regions were un-warped from MNI space to each subject's structural image, using a 12 parameter co-registration method.

To assess whether the imagery tasks produced the expected activations in pre-defined neuroanatomical locations, two contrasts were performed for each participant; namely, motor minus spatial imagery, and its reverse. The multiple localizer sessions of the patient were averaged using a fixed-effects model.

'Answers' in the communication scans were assessed using a two-step procedure. First, activity in the two ROIs during the motor and spatial imagery localizer scans was quantitatively characterized (using the average GLM estimate for each ROI). Next, a similarity metric (*relative similarity;* see Appendix) was computed to quantify how closely the activity in the ROIs for question scans matched each localizer.

Results

fMRI Assessment: Imagery task. Of 54 patients, five could willfully modulate their brain activity (see Figure 1). In all five cases, the motor minus spatial imagery contrast resulted in significant activation in the SMA. In 4 out of 5 patients, the spatial minus motor imagery contrast also revealed consistent activation in PPA. Furthermore, the time-course of activity within the two ROIs was sustained across a period of 30 seconds and time-locked to the delivery of the verbal cues (see Figure 2). These results closely match the pattern observed in the healthy volunteers (Figure 1; see also Appendix). Four of the five patients were admitted with a VS diagnosis (including patient C04 who has been previously reported[10]) and all five had suffered a traumatic brain injury (see Table 1).

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fMRI Assessment: Communication task. Each of the 16 healthy volunteers underwent 3 question scans. For all 48 questions, the correct answer was determined with 100% accuracy by comparing activations in question scans to the two localizers. In all cases, the pattern produced in response to each question was (quantitatively) more similar to the pattern observed, in localizer scans, for the imagery task associated with the factually correct answer (which was verified *after* the analysis). This similarity is illustrated, in a sample healthy volunteer, in Figures 2b,d and 3b,d. In this participant (see Figure 4), the comparison of imagery minus rest in Question 1 yielded extensive SMA activation coupled with minimal PPA activity. This pattern was almost identical to that observed in the tennis minus rest contrast for the motor localizer. Conversely, the imagery minus rest contrasts in Questions 2 and 3 revealed extensive PPA and, to a lesser extent, SMA activation, closely matching the activation seen in the spatial localizer. Similar patterns were observed in 9 out of 16 volunteers. For the remaining 7 participants the distinction between tasks was even clearer; thus, a double dissociation was observed between SMA activity for tennis and PPA activity for spatial navigation (see Appendix).

To assess whether such an approach could be employed in a patient with impaired consciousness, one of the patients (L23) who had produced reliable responses during the two imagery tasks was also asked 6 'yes/no' autobiographical questions and instructed to respond by producing one type of imagery for an affirmative answer, and the other for a negative one.

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In response to 5 of the 6 question scans, the activity observed in the patient closely matched that observed in one of the localizer scans (Figure 2a,c and 3a,c). For example, in response to the question "Is your father's name Alexander?", the patient responded 'yes' (correctly) by producing activity that matched that observed in the motor imagery localizer (Figure 3a). On the other hand, in response to the question "Is your father's name Thomas?", the patient responded 'no' (also correctly) by producing activity that matched that observed in the spatial imagery localizer (Figure 3c).

The relative similarity analysis confirmed, quantitatively, that the activity observed during question scans accurately reproduced that observed during localizer scans within the bounds of normal variability for 5 out of the 6 questions (Figure 4; see also online only Tables A1 and A2). In addition, for those same 5 questions the pattern produced always matched the factually correct answer. Only one question, the last one, could not be decoded. However, this was not because the "incorrect" pattern of activation was observed, but rather, because virtually no activity was observed within the ROIs at all.

Discussion

In this study, fMRI was used to determine the incidence of undetected awareness in a group of patients with severe brain injuries. Of 54 cases, 5 patients with traumatic brain injuries were able to modulate their brain activity by generating voluntary, reliable and repeatable blood oxygenation level dependent (BOLD) responses in predefined neuroanatomical regions when prompted to perform imagery tasks. No such responses were observed in any patient with a non-traumatic brain injury. Four of these cases were admitted as VS. When thoroughly retested, some behavioral indicators of awareness could be detected at the bedside in two of these patients. However, the other two patients remained behaviorally non-responsive at the bedside, even after the fMRI results were known and despite repeated testing by a multidisciplinary team. This confirms that, in a minority of cases, residual cognitive function and even conscious awareness can exist in patients who fulfill the behavioral criteria for VS [14,15].

Additional tests were conducted on one of the five patients with evidence of awareness on fMRI and he demonstrated ability to apply the imagery technique to answer simple 'yes/no' questions accurately. Prior to scanning, the patient had been repeatedly diagnosed as vegetative, including a month-long specialized assessment by a highly trained clinical team. At the time of scanning, however, thorough retesting at the bedside did show reproducible but highly fluctuating and inconsistent signs of command following (see Appendix), consistent with an MCS diagnosis. Nonetheless, despite the best efforts of the clinical team, it was impossible to establish any functional communication at the bedside, and the behavioral examination remained marred by ambiguity and inconsistency. In contrast, the fMRI approach allowed him to establish functional and interactive communication. Indeed, in all cases where a reliable neural response could be detected (5 out of 6 questions), the patient was able to provide the correct answer with 100% accuracy. In response to the remaining question – the last of the imaging session – the absence of activity within the ROIs precluded any analysis of the results. Whether the patient fell asleep during this question, failed to hear it, simply elected not to answer it, or lost consciousness can not be determined.

While the fMRI data provided clear evidence that the patient was aware and able to communicate, it is not known whether either ability was available during earlier evaluations. It is possible that the patient was vegetative when diagnosed at 17 months and 3.5 years post-injury and subsequently regained some aspects of cognitive functioning. Alternatively, the patient may have been aware during previous assessments, but unable to produce the necessary motor response required to signal his state of consciousness. If this was the case, then the clinical diagnosis of VS was procedurally entirely accurate in the sense that no behavioral markers of awareness were evident. That said, it did not accurately reflect this patient's internal state of awareness and level of cognitive functioning at the time. Given that all prior assessments were based on behavioral observations alone, these two possibilities are indistinguishable.

For 49 of the 54 patients included in this study, no significant fMRI changes were observed during the imagery tasks. In these cases, it is not possible to determine whether the negative findings are the result of low "sensitivity" of the methodology (e.g. to detect small effects), or genuinely reflect the patients’ limited cognitive abilities. Some patients, for example, may have been unconscious (permanently or transiently) during scanning. Similarly, in some awake and aware MCS patients, the tasks may simply have exceeded their residual cognitive capabilities. Deficits in either language comprehension, working memory, decision-making or executive function would prevent successful completion of the imagery tasks. On the other hand, positive results, whether observed with or without corroborative behavioral data, do confirm that all such processes are intact and that the patient must be aware.

In summary, the results of this study demonstrate the potential for fMRI to bridge the dissociation that can occur between behavior that is readily observable during a standardized clinical assessment and the actual level of residual cognitive function following serious brain injury.[14-16] Thus, of 23 patients who were diagnosed as vegetative at the point of admission, four were shown to be able to willfully modulate their brain activity through mental imagery, a fact that is entirely inconsistent with that (behavioral) diagnosis. In two of these cases, however, subsequent assessment at the bedside revealed some behavioral evidence of awareness, emphasizing the importance of thorough clinical examination in this patient group for reducing misdiagnosis. Nonetheless, for the two remaining patients, no evidence of awareness could be detected at the bedside by an experienced clinical team, even after the results of the fMRI examination were known. This finding demonstrates that, in some cases, motor function can be so impaired that bedside assessments based on behavior are unable to detect awareness, regardless of how thoroughly and carefully they are administered. In this context, it is clear that fMRI complements existing diagnostic tools by providing a method for detecting covert signs of residual cognitive function[17-20] and awareness[10] in behaviorally non-responsive patients.

This study also demonstrated in one patient with severe impairment of consciousness that fMRI can also be used to communicate solely by modulating brain activity. In contrast, no communication could be established at the bedside. In future, this approach could be used to address important clinical questions. For example, patients could be asked if they are feeling any pain, thus guiding the administration of analgesics where necessary. Extensions of this technique could be used by some patients to express their thoughts, control their environment and increase their quality of life.

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Table 1. *Patient data.* Details of the patients who underwent the tennis and navigation imagery tasks in Liege (L##) and Cambridge (C##) over a three year period. In the last two columns, the '+' sign indicates a successfully performed task, '-' denotes an unsuccessfully performed task, while a blank space indicates the task was not performed (or not analyzable due to excessive movement). We highlight in bold the only patient who underwent the communication paradigm (L23).

	Diagnosis on Admission	Age	Aetiology	Gender	Time post ictus (months)	Motor Imagery Loc.	Spatial Imagery Loc.
C01	VS	58	TBI	M	6.0	-	-
C02	VS	43	Anoxic	F	50.0	-	-
C03	VS	41	TBI	F	10.0	-	
C04	VS	23	TBI	F	6.0	+	+
C05	VS	42	Anoxic	M	8.0	-	-
C06	VS	46	TBI	M	2.0	+	-
C07	VS	52	Anoxic/Encephalitis	F	8.0	-	
C08	VS	23	TBI	M	19.0	-	-
C09	VS	48	Anoxic	F	18.0	-	-
C10	VS	34	TBI	M	13.0	-	-
C11	VS	35	Anoxic	M	10.0	-	-
C12	VS	29	TBI	M	11.0	-	-
C13	VS	67	TBI	M	14.0	-	-
C14	VS	21	TBI	M	6.0	-	-
C15	VS	49	TBI	M	3.0	-	
C16	VS	56	Anoxic	F	9.0	-	-
L01	VS	87	CVA	M	<1.0	-	-

L02	VS	62	CVA	M	1.0	-	-
L03	VS	15	Anoxic/TBI	M	20.5	-	-
L04	VS	70	Meningitis	F	2.5	-	-
L05	VS	47	Anoxic	M	18.8	-	-
L22	VS	22	TBI	F	30.2	+	+
L23	**VS**	**22**	**TBI**	**M**	**60.8**	+	+
C23	MCS	23	TBI	M	11.0	-	-
C24	MCS	38	TBI	F	3.0	-	
C25	MCS	18	TBI	M	8.0	-	-
C26	MCS	26	TBI	M	11.0	-	
C27	MCS	64	TBI	M	6.0	-	-
C28	MCS	54	Brainstem stroke	F	5.0	-	-
C29	MCS	29	TBI	F	2.0	-	
C30	MCS	19	TBI	F	1.0	-	-
C31	MCS	34	TBI	M	52.0	-	
C32	MCS	17	TBI	M	7.0	-	
C33	MCS	56	Anoxic	M	6.0	-	-
C34	MCS	21	TBI	M	51.0	-	-
C35	MCS	53	Anoxic	F	13.0	-	-
C36	MCS	36	TBI	M	30.0	-	
C37	MCS	25	TBI	M	8.0	-	-
L06	MCS	64	Meningitis	F	<1.0	-	-
L07	MCS	37	TBI	M	11.4	-	-
L08	MCS	70	Meningitis	M	1.3	-	-
L09	MCS	36	TBI	M	4.5	-	-
L10	MCS	49	TBI	M	0.4	-	-
L11	MCS	49	TBI	M	1.6	-	-
L12	MCS	19	TBI	M	1.3	-	-

L13	MCS	26	Anoxic	M	42.4	-	-
L14	MCS	49	Anoxic	F	84.7	-	-
L15	MCS	55	Anoxic	M	1.0	-	-
L16	MCS	28	TBI	M	72.3	-	-
L17	MCS	49	Anoxic	F	84.7	-	-
L18	MCS	49	Anoxic	M	0.8	-	-
L19	MCS	39	Anoxic	M	308.9	-	-
L24	MCS	23	TBI	M	10.0	-	-
L25	MCS	27	TBI	M	1.3	+	+

FIGURE LEGENDS

Figure 1. *Mental imagery task.* Results for the motor versus spatial (yellow-red) and spatial versus motor (blue) imagery contrasts for healthy volunteers (N = 16) and 5 patients with disorders of consciousness (see Table 1 for patient details). [TBI - traumatic brain injury.]

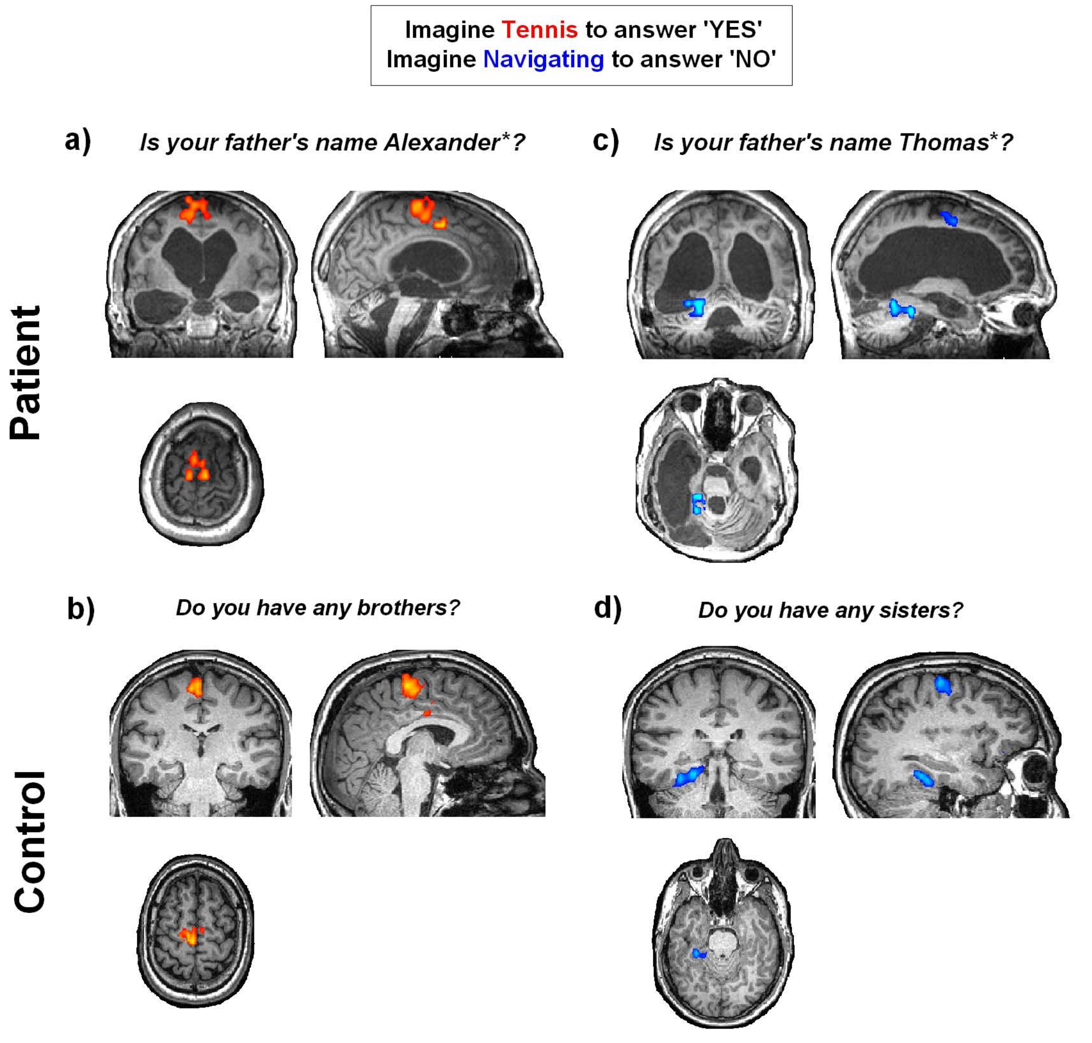
Figure 2. *Localizer scans.* Imaging results for the patient (masked by the healthy volunteer group ROI, see methods) and a representative healthy volunteer. Panels a) and b) depict the result for the motor imagery minus rest contrast, as well as the time-course of the peak voxel in the SMA for the patient and the control, respectively. Panels c) and d) depict the result for the spatial imagery minus rest contrast, as well as the time-course of the peak voxel in the PPA for the patient and the control, respectively.

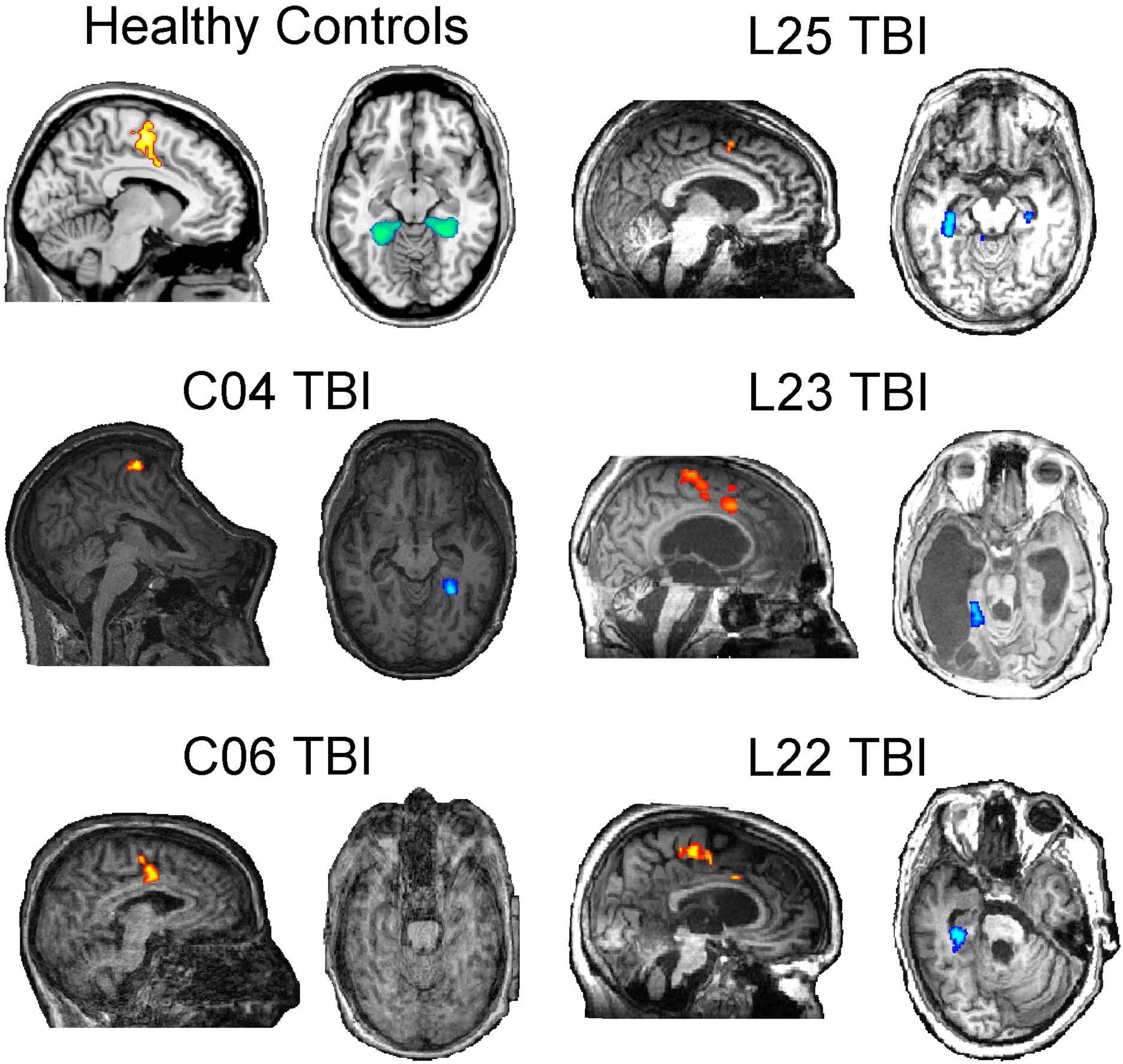
Figure 3. *Question Scans.* Imaging results from two sample questions scans for the patient and a healthy volunteer. Panels a) and b) depict two question scans in which the observed activity pattern was very similar to that observed in the tennis imagery localizer (i.e. activity in SMA alone – see Figure 1), indicating a 'yes' response. Panels c) and d) depict two question scans in which the observed activity pattern was very similar to that observed in the navigation imagery localizer (i.e. activity in both PPA and SMA - see Figure 1), indicating a 'no' response. (* The names in this figure have been changed to retain anonymity.)

Figure 4. *ROI Data.* Pattern of activation for the SMA (red) and PPA (blue) ROIs in the localizer and question scans for the patient (6 questions) and a sample healthy volunteer

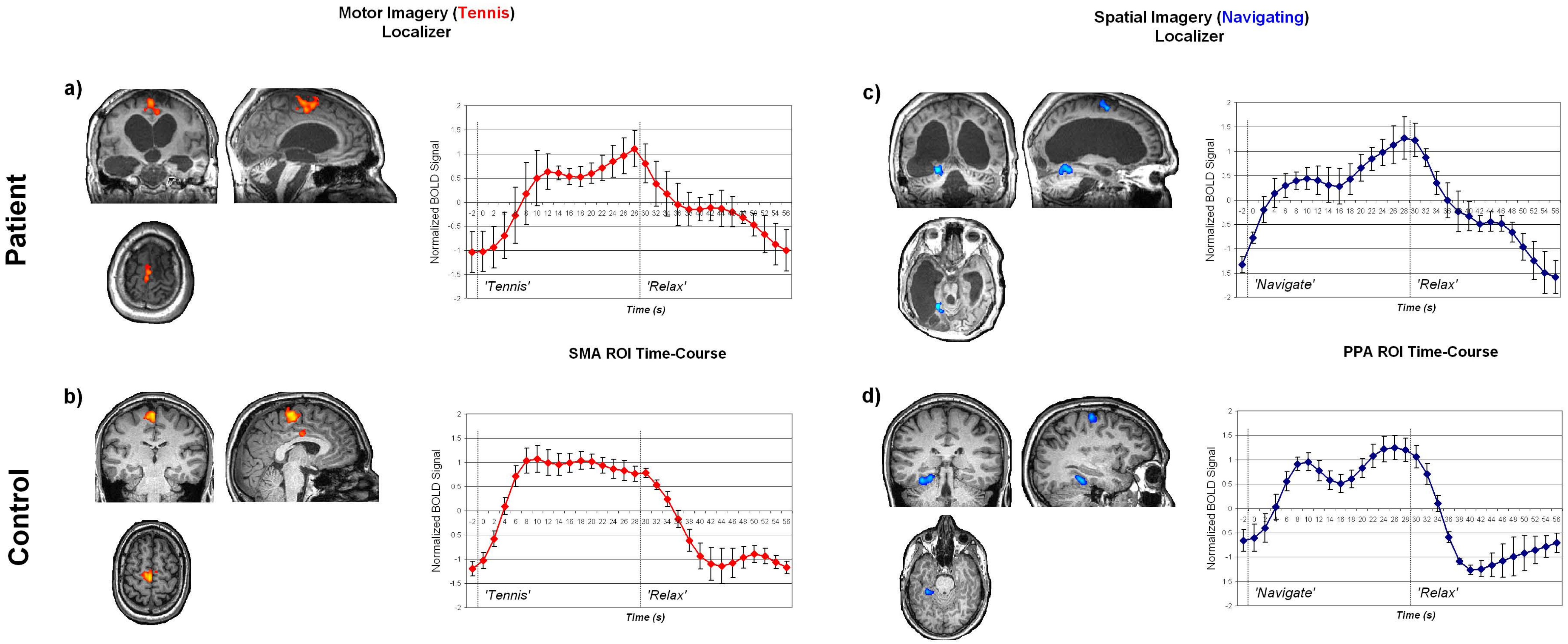
(3 questions).

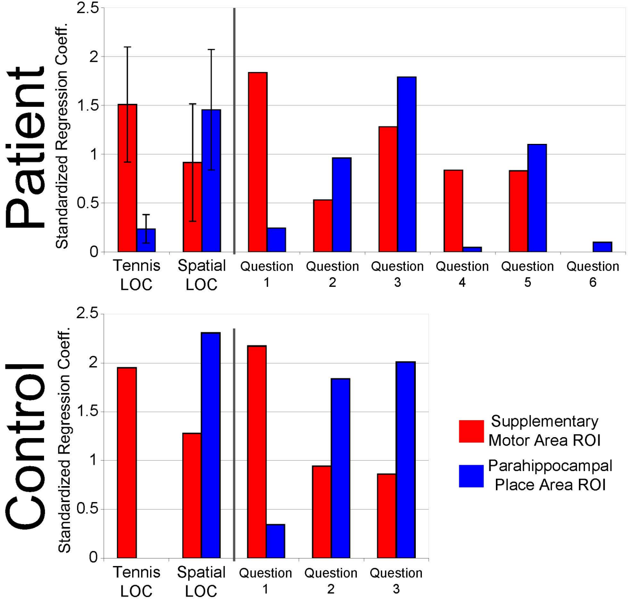
Sample Question Scans




Healthy Controls
L25 TBI
C04 TBI
L23 TBI
C06 TBI
L22 TBI

Localizer Scans




Patient
Standardized Regression Coeff.
2.5
2
1.5
1
0.5
0
Tennis LOC
Spatial LOC
Question 1
Question 2
Question 3
Question 4
Question 5
Question 6
Control
Standardized Regression Coeff.
2.5
2
1.5
1
0.5
0
Tennis LOC
Spatial LOC
Question 1
Question 2
Question 3
Supplementary Motor Area ROI
Parahippocampal Place Area ROI

Online Appendix for:

Willful modulation of brain activity and communication in disorders of consciousness

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This document includes:

1. Inclusion Criteria

Both the Cambridge and the Liege sites routinely admit brain injury patients (VS and MCS) for evaluation with fMRI, from a network of referring centers. In both locations, patients are neither pre-selected nor pre-screened on the basis of bedside examinations. The main constraint to admitting a patient is where they require paramagnetic medical apparata that may not be suitable for entering the fMRI environment. In addition, in Cambridge, patients that appear clearly hyperkinetic and unlikely to remain sufficiently still throughout the imaging session are, when such a situation is evident, not admitted. In Liege, patients undergo structural scanning under sedation. Many of these patients, however, during the functional scans (when they are not sedated) exhibit excessive movements (several centimeter), rendering the data not analyzable.

2. fMRI Data Acquisition Parameters and Pre-Processing

fMRI Data Acquisition. Volunteer data was collected at the MRC Cognition and Brain Sciences Unit, Cambridge (UK) on a 3T Tim Trio Siemens system. Patient data was collected at the Wolfson Brain Imaging Centre, Cambridge, on a 3T Siemens Tim Trio and a 3T Brucker system, and at the Liège University Hospital (Belgium) on a 3T Siemens Allegra. T1-weighted images were acquired with a 3D MP-RAGE sequence (TR 2300 ms, TE 2.47 ms, TI 900 ms, 150 slices, 1x1x1.2 mm resolution). T2* sensitive images were acquired using an echo planar sequence (TR = 2000 ms, TE = 30 ms, 32 descending axial slices, 3x3x3.75 mm resolution on the Siemens machines, and TR = 1100 ms, TE 27.5 ms, 21 interleaved transverse slices, 4 mm thickness on the Bruker system).

fMRI Data pre-processing. Analysis methods were performed using FSL 4.1 (FMRIB Software Library, Oxford University).[1] Prior to functional analyses, a series of pre-processing steps were performed. First, signal from extraneous non-brain tissue was removed using BET (Brain Extraction Tool).[2] Each individual echo planar imaging (EPI) time-series was motion corrected to the middle time point using a 6 parameter, rigid-body method (as implemented in MCFLIRT).[3] Data were then band-pass filtered (2.8 – 60 s) and smoothed using a Gaussian kernel of 5 mm FWHM. Autocorrelation was corrected with a pre-whitening technique (as implemented in FEAT; fMRI Expert Analysis Tool).[4]

3. Relative Similarity Metric

Similarity of brain activation between question and localizer scans was assessed according to the Euclidean distance. Specifically, activity in each scan was re-described as a point within a two dimensional plane with axes corresponding to the activation seen in each ROI (SMA, PPA). If one defines *total distance* as the sum of the distances separating a given question scan from the two localizers, the *relative similarity* (rs) between a given question and each localizer is equal to one minus the ratio of the distance between the question and each localizer, and the total distance. For example, the relative similarity of a given question Qi to each localizer (tennis localizer, TL; and navigation localizer, NL) can be obtained as follows (with d(x,y) representing the Euclidean distance separating point x from point y):

$$rs(Q_i,TL) = 1 - \left(\frac{d(Q_i,TL)}{d(Q_i,TL) + d(Q_i,NL)} \right)$$

$$rs(Q_i,NL) = 1 - \left(\frac{d(Q_i,NL)}{d(Q_i,TL) + d(Q_i,NL)} \right)$$

In two-dimensional space, the smaller the distance separating a question and a localizer scan, the greater the relative similarity.

4. Healthy Volunteer Results

Analysis of the localizer data for each healthy volunteer revealed two consistent patterns of activity in response to motor and spatial imagery. For 7 out of 16 volunteers, each ROI selectively responded to just one type of imagery, with the SMA responding to motor imagery only and PPA responding to spatial imagery only. For the remaining 9 volunteers, motor imagery activated the SMA alone, but spatial imagery activated both the PPA and, to a lesser extent, the SMA. Noticeably, whichever pattern was detected in the localizers, that same pattern was observed during the question scans. The similarity analysis successfully 'decoded', with 100% accuracy, the answer provided by modulation of brain activity alone to each of the 48 questions (3 questions per subject). Indeed, the pattern of ROI activation in each question scan was always more similar to the imagery task associated with the factually correct answer (see Table A1).

Table A1. Relative similarity data for 16 healthy volunteers. (In bold the imagery task that corresponded, for each question, to the correct answer.)

		% Similarity to Localizers		
		Question 1	Question 2	Question 3
sub 1	Motor Imagery Localizer	**84.65**	14.94	14.96
	Spatial Imagery Localizer	15.35	**85.06**	**85.04**
sub 2	Motor Imagery Localizer	**94.23**	25.89	**81.03**
	Spatial Imagery Localizer	5.77	**74.11**	18.97
sub 3	Motor Imagery Localizer	**80.01**	29.92	**82.30**
	Spatial Imagery Localizer	19.99	**70.08**	17.70
sub 4	Motor Imagery Localizer	22.32	**88.83**	**81.76**
	Spatial Imagery Localizer	**77.68**	11.17	18.24
sub 5	Motor Imagery Localizer	27.26	**84.73**	**64.93**
	Spatial Imagery Localizer	**72.74**	15.27	35.07
sub 6	Motor Imagery Localizer	12.83	**81.66**	23.42
	Spatial Imagery Localizer	**87.17**	18.34	**76.58**
sub 7	Motor Imagery Localizer	**82.84**	38.66	30.56
	Spatial Imagery Localizer	17.16	**61.34**	**69.44**
sub 8	Motor Imagery Localizer	25.92	13.18	**86.72**
	Spatial Imagery Localizer	**74.08**	**86.82**	13.28
sub 9	Motor Imagery Localizer	14.94	**65.39**	11.83
	Spatial Imagery Localizer	**85.06**	34.61	**88.17**
sub 10	Motor Imagery Localizer	**87.17**	**77.99**	13.02
	Spatial Imagery Localizer	12.83	22.01	**86.98**
sub 11	Motor Imagery Localizer	**85.50**	**88.33**	5.68
	Spatial Imagery Localizer	14.50	11.67	**94.32**
sub 12	Motor Imagery Localizer	**84.26**	17.92	**87.28**
	Spatial Imagery Localizer	15.74	**82.08**	12.72
sub 13	Motor Imagery Localizer	**83.76**	17.87	17.27
	Spatial Imagery Localizer	16.24	**82.13**	**82.73**
sub 14	Motor Imagery Localizer	**92.84**	12.86	8.61
	Spatial Imagery Localizer	7.16	**87.14**	**91.39**
sub 15	Motor Imagery Localizer	**96.92**	11.11	38.42
	Spatial Imagery Localizer	3.08	**88.89**	**61.58**
sub 16	Motor Imagery Localizer	**78.64**	12.12	**67.44**
	Spatial Imagery Localizer	21.36	**87.88**	32.56

5. Similarity Analysis Results for the Patient.

Table A2. Relative similarity data for the patient. (In bold the imagery task that corresponded, for each question, to the correct answer.)

		% Similarity to Localizers					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
Patient	Motor Imagery Localizer	33.93	24.01	**82.31**	**66.89**	24.88	**51.93**
	Spatial Imagery Localizer	**66.07**	**75.98**	17.69	33.11	**75.12**	48.07

6. Voluntary vs. Automatic Brain Responses

Is there any possibility that this patient was not conscious, yet able to generate appropriate answers to autobiographical questions 'automatically' in response to the questions? Recent evidence suggests that single words can, under certain circumstances, elicit wholly automatic neural responses in the absence of conscious awareness. However, such responses last for a few seconds at most and, unsurprisingly, occur in regions of the brain that are associated with word processing.[5] In contrast, the responses in the patient presented here were sustained across the 30 sec epochs in the absence of any further stimulation and were observed in regions that are known to be involved in the two imagery tasks.[6,7] More importantly, in the current study, the same neutral word ('*answer'*) was used to cue a response, irrespective of which imagery task was to be performed. This precludes any possibility that the observed activity occurred automatically (i.e. in the absences of awareness) since in different questions an identical cue yielded different, yet predicted, BOLD responses. These responses could, therefore, only depend on the patient's conscious decision (or 'mindset') about which answer to give (see also ref. 8 for discussion).

With respect to the novel communication method presented in the main text, in order to 'answer' a question, the patient was first required to select which of the two imagery tasks was appropriate for the answer that he intended to give ('yes' or 'no') and to engage in that type of imagery when cued with the word '*answer*' and disengage (or relax) when cued by the word *'relax*.' Each period of imagery required his sustained involvement in the task in order to generate continuous activity in the target ROI across each 30 second epoch. Moreover, in order for a statistically reliable '*answer*' to be detectable he was required to repeat each imagery task 5 times (per question).

Sustained, time-locked and repeated activity within well characterized neuroanatomical regions requires a level of cognitive processing that includes language comprehension, memory, attention and voluntary or 'willful' behavior.

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